

REMARKS

Claims 1 and 4-21 are pending in this application. Claims 2 and 3 have been canceled without prejudice or disclaimer. Claims 1, 7, 12, 18, and 20 have been amended to recite “TFPI or ala-TFPI” instead of “TFPI or TFPI variant.”

No new matter has been added.

Information Disclosure Statement

A copy of the PTO/SB/08A form filed July 15, 2004 and copies of the cited references accompany this paper. Applicants respectfully request that the Examiner consider the cited references and return an initialed copy of the form with the next Office Action.

The Rejections of Claims 1-21 under 35 U.S.C. § 112, ¶ 1

Claims 1-21 stand rejected under 35 U.S.C. § 112, ¶ 1 as neither enabled nor described. Applicants respectfully traverse these rejections insofar as they apply to pending claims 1 and 4-21, as now amended.

To advance prosecution Applicants have amended the pending claims to recite subject matter that the Office Action explicitly recognizes as satisfying the enablement and written description requirements of 35 U.S.C. § 112, ¶ 1. That is, in addition to TFPI, the pending claims now recite “ala-TFPI” instead of “TFPI variant.” The Office Action states that the specification is enabling for and describes a lyophilized composition comprising ala-TFPI. See the Office Action, page 2, 1st paragraph of item 6; page 4, 2nd paragraph of item 7. TPFI, of course, is a protein that is well-known and well-characterized in the art. See paragraphs [03] to

[05] of the specification. Applicants therefore respectfully submit that the specification is enabling for and describes TFPI.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, ¶ 1 are respectfully requested.

The Rejection of Claims 1-21 Under 35 U.S.C. § 103(a)

Claims 1-21 stand rejected as obvious over Andya *et al.*, U.S. Patent 6,267,958 (Andya) in view of Chen *et al.*, U.S. Patent 5,888,968 (Chen). Applicants respectfully traverse this rejection.

Amended independent claims 1, 7, 18, and 20 recite lyophilized compositions comprising TFPI (SEQ ID NO:1) or ala-TFPI. The lyophilized compositions also comprise a carbohydrate or amino acid glass forming agent (claims 1 and 7), a citrate buffer (claim 18), or sulfate and a phosphate buffer (claim 20). The Office Action cites Andya as teaching various stable lyophilized formulations and cites Chen as teaching various TFPI pharmaceutical compositions. The Office Action contends, “It would have been obvious . . . to employ TFPI composition[s] taught by Chen *et al.* in the stable lyophilized formulation taught by Andya *et al.* to increase storage time and multi-use formulation (Andya, col. 1, lines 51-60).” See the Office Action, page 6, 7th paragraph of item 9.

A *prima facie* case of obviousness requires a showing that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contains a suggestion or motivation to combine the reference teachings. Also, there must be a reasonable expectation of success in making the proposed combination. M.P.E.P. § 2142. These

requirements of a *prima facie* case of obviousness under 35 U.S.C. § 103 are not met. That is, there would have been no motivation to combine the teachings of Andya with Chen and no reasonable expectation that such a combination would have been successful.

Andya purports to address the known problems associated with highly concentrated protein formulations, namely their tendency to aggregate during processing. Col. 21, line 19 to col. 22, line 36. Andya's solution is to lyophilize proteins that can be reconstituted into aqueous formulations having high protein concentration without significant instability. See the abstract and reconstitution diluents which provide hydration (col. 17, lines 22-29). The proteins taught in Andya to benefit from lyophilization are highly soluble in aqueous solutions (*i.e.*, they are capable of being concentrated in aqueous solutions to 50 mg/ml or more). Col. 2, lines 3-7: "In particular, while the protein concentration in the pre-lyophilized formulation may be 5 mg/ml or less, the protein concentration in the reconstituted formulation is generally 50 mg/ml or more." The reconstituted, aqueous formulations of Andya can have "significantly higher (*e.g.*, from about 2-40 times higher. . .) [protein concentration] than the protein concentration in the pre-lyophilized formulation." Col. 1, line 67 to col. 2, line 3. In fact, Andya consistently describes the aqueous reconstituted formulations as having protein concentrations of at least about 50 mg/ml. See for example, col. 2, lines 30-34 and 39-41. Particular disclosed ranges of "high protein concentrations in the reconstituted formulation" are as high as 50-400 mg/ml, 80-300 mg/ml, and 90-150 mg/ml. See col. 17, lines 1-11. In view of these teachings of Andya, one of ordinary skill would not expect a highly insoluble protein such as TFPI to benefit from lyophilization.

From reading Chen, one of ordinary skill in the art would readily recognize the severe solubility limitations of TFPI in aqueous solution. See Chen, col. 2, lines 27-28: “TFPI is a hydrophobic protein and as such, has very limited solubility in aqueous solutions.” In fact, in recognizing the severe solubility limitations of TFPI in aqueous solution, as taught in Chen, one would have been discouraged from combining Chen’s teachings with those of Andya.

Chen’s solution for overcoming this poor solubility is based on Chen’s findings that certain solubilizers can be used to achieve TFPI concentrations of more than 0.2 mg/ml. Col. 2, lines 38-50. Based on Figs. 1-3 of Chen, the solubility of TFPI can be increased under conditions of high pH (*e.g.*, above 10) or in the presence of high concentrations of citrate or NaCl, but even then only to a maximum of about 15 mg/ml. Therefore, from the disclosure of Chen, it would have been apparent that Andya’s “high protein concentrations in the reconstituted formulation” of 50-400 mg/ml are not even possible in aqueous TFPI solutions. The ordinary skilled artisan would not have been motivated to take TFPI, described in Chen as being a very insoluble protein, and lyophilize it in an effort to achieve the “significantly higher” protein concentrations taught in Andya.

There is no teaching, suggestion, or motivation to combine the teachings of Chen with the teachings of Andya, as proposed in the Office Action. For the same reasons, it would not have been reasonable to expect that the TFPI formulations described in Chen would benefit from lyophilization as taught in Andya.

Unexpectedly, in view of the teachings of Chen and Andya, Applicants discovered that TFPI aggregation actually increases (and consequently stability decreases) as TFPI concentration is reduced. See paragraphs [98] and [120] of the specification. Applicants recognized that TFPI,

despite its limited solubility (and consequently its inability to be significantly concentrated), can benefit from lyophilization, especially at low concentrations. In fact, in preferred embodiments described in paragraph [32] (to which the subject matter of claim 12 is directed), the aqueous formulation comprises no more than about 10 mg/ml, no more than about 1 mg/ml, or no more than about 0.2 mg/ml TFPI, prior to lyophilization.

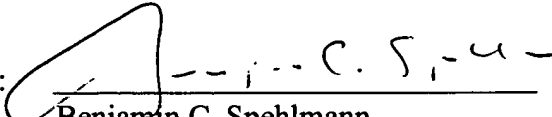
Any assertion that it would have been obvious to combine the teachings of Andya and Chen to arrive at the claimed invention is based purely on hindsight analysis, using Applicants' own teachings for guidance. It is black letter law that hindsight use of the specification is not permitted. *Texas Instruments Inc. v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

For the reasons stated above, the Office Action fails to make out a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection is respectfully requested.

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Respectfully submitted,
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